RESEARCH PROPOSAL

Herb Drug Interaction Study between Common Oral Antidiabetic Drug and Extracts of Antidiabetic *Prosopis* species

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Ritu Jangid
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Under the Supervision of

Dr. Sreemoyee Chatterjee

Associate Professor

Department of Biotechnology

DEPARTMENT OF BIOTECHNOLOGY

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Introduction

India is facing a growing burden of diseases. In 2016, the Non - Communicable diseases (NCDs) caused 71% (41 million) total deaths globally. The Global burden of disease (GBD), data reported that diabetes is the major cause of death in India (Tandon et al., 2018). It is the most common metabolic disease worldwide and about 150 million people suffer from this disease (Mastor, 2020). It shows hypoglycemic defects resulting in inappropriate development of insulin secretion, which can cause long term damage, dysfunction, and failure of body organs (Diabetes, 2010). Different Oral Antidiabetic drugs and insulin are the main allopathic medications available for the treatment of diabetes (Mastor, 2020). Over millions of Indians also consume herbal medicines as dietary supplements in the form of spices and home- remedies to cure diabetes (Vaidya & Devasagayam, 2007). According to WHO, 70% of the world's human population use herbs as alternative medicine (Shaikh et al., 2020). Patients with diabetes frequently prefer concomitant administration of traditional herbal plants with allopathic medicine without consulting with their healthcare providers. This combined administration of herb with therapeutic drugs alters the drug concentration level in the human body and raises the potential of herb-drug interaction (Shaikh et al., 2020). Herb drug interaction is an important mechanism to create awareness among people about the risk factors of combination therapy (Fasinu et al., 2012). This process alters the pharmacodynamic and pharmacokinetic properties of the drug and causes drug toxicity. Pharmacodynamic herb-drug interaction produces changes in the pharmacological effects through additive, synergistic, and antagonistic actions of the drug (Nanjappan et al., 2018). It also alters the mechanism and the concentration level of a coadministered drug (Mamindla et al., 2016). Pharmacokinetic interaction involves alteration in absorption, distribution, metabolism, and excretion (ADME) of the drug which results in changing the drug metabolite levels (Nanjappan et al., 2018). In pharmacokinetic interactions, there is an inhibition or induction of drug-metabolizing enzymes (DMEs) mainly Cytochrome P450 (CYP) and drug transporters such as P-gp which results in increasing or decreasing plasma levels of the drug (K. Kapoor & Singla, 2015). It is estimated that most of the herb-drug interaction studies focus only on the pharmacokinetic properties of the drug as compared to pharmacodynamic activity (Zuo et al., 2015). This research proposal illustrates the herb-drug interaction of commonly used medicinal herbs of *Prosopis* species with Oral Antidiabetic allopathic medicines.

Review of literature

Diabetes Mellitus –

Diabetes mellitus is commonly known as diabetes is a common metabolic disease in the world (Diabetes, 2010). Globally around 150 million people are suffering from this disease (Mastor, 2020). Diabetes shows hypoglycemic defects resulting in inappropriate development of insulin secretion, which can cause long term damage, dysfunction, and failure of body organs (Diabetes, 2010). In this disease, there is the destruction of the beta cells of the pancreas results in impairment of insulin secretion and immune system regulation. Diabetes can be of 3 types - type 1 diabetes, type 2 diabetes, and gestational diabetes (Mastor, 2020). Type 1 diabetes is an autoimmune disease, commonly occurs during childhood and adolescence (Kahanovitz et al., 2017). It is also known as insulin-dependent diabetes in which patients are not able to produce their insulin as their body attacks the pancreas (Cox-Georgian et al., 2019). Type 2 diabetes is known as non-insulin-dependent diabetes (Olokoba et al., 2012). Patients with type 2 diabetes can't use the insulin made by their bodies, or their bodies are not able to produce enough insulin (Cox-Georgian et al., 2019). According to WHO, gestational diabetes is the disease first detected during pregnancy. This disease has a high risk of developing type 2 diabetes in mother and foetus later in life (Mirghani Dirar & Doupis, 2017). Symptoms in diabetic patients are polyuria, polydypsia, weight loss, polyphagia, blurred vision, renal failure, foot ulcers, sexual dysfunction, cerebrovascular diseases, hypertension, abnormal metabolizing of lipoprotein, and fatigue (Diabetes, 2010). Positive family history of diabetes, increasing age, overweight & obesity, enlarge waist, hypertension, sedentary lifestyle and gestational diabetes are considered as the main risk factors of diabetes mellitus (Ramachandran et al., 2005). Screening test of diabetes includes Oral Glucose Tolerance Test (OGTT), Glycosylated Haemoglobin (HbA1c), random plasma glucose (RPG), random blood glucose, fasting plasma glucose (FPG), and fasting blood glucose (FBG), etc. (Adepoyibi et al., 2013). Insulin and hypoglycemic drugs are the main medications available for DM (Mastor, 2020). 6 classes of Antidiabetic/hypoglycemic drugs involved in treating DM includes Biguanides (e.g., metformin), sulfonylureas (e.g., glimepiride), meglitinides (e.g., repaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors (e.g., sitagliptin), and α-glucosidase inhibitors (e.g., acarbose) (Chaudhury et al., 2017).

Oral Antidiabetic drug classes -

Drug class		Agent
Biguanides		Metformin
Sulfonylureas	*first generation*	Acetohexamide
		Chlorpropamide
		Tolazamide
		Tolbutamide
	second generation	Glibenclamide/Gliburide
		Glipizide
		Glimepiride
		Gliclazide
Meglitinides		Repaglinide
		Nateglinide
Thiazolidinediones		Rosiglitazone
		Pioglitazone
α-Glucosidase inhibitors		Acarbose
		Miglitol
Incretin agonists		Exenatide
		Liraglutide
DPP-4 inhibitors		Sitagliptin
		Vildagliptin
		Saxagliptin

Source-https://www.semanticscholar.org/paper/Oral-Hypoglycemic-Drugs%3A-Pathophysiological-Basis-Lorenzati-Zucco/f08f83207cf30faf00ec9b320ef5721fec130f4b

Meglitinides –

Meglitinides are short, rapid, insulinotropic anti- diabetic agents used to treat type 2 diabetes mellitus (T2DM). They are secretagogue molecules with more rapid anti-hyperglycemic action and have valuable roles in lowering postprandial hyperglycemia and reducing the danger of hypoglycemia (Guardado-Mendoza et al., 2013). Repaglinide and Nateglinide are the 2 brands of meglitinide oral Antidiabetic drugs. (Wu et al., 2017). The mechanism of action of meglitinide is to stimulate insulin release by blocking ATP –dependent K channels in pancreatic beta cells, inhibits KATP channels resulting in membrane polarization and calcium influx through voltage-gated calcium channels (mechanism is similar to that of sulfonylureas). Repaglinide is the first meglitinide oral antidiabtic drug used to treat type 2 diabetes mellitus. It binds to sulphonylurea receptors as well as other distinct receptors and blocks the ATP- dependent potassium channels (KATP) of the pancreatic β-cell, resulting depolarizing of membrane which opens voltage-gated calcium channels to allow calcium influx thus leads insulin secretion. It is rapidly absorbed with 63% bioavailability. Volume of distribution is small (Highly bound to plasma albumin) It is metabolism by CYP3A4 in liver and eliminated by biliary tract (Guardado-Mendoza et al., 2013)

Nateglinide also binds to sulphonylurea receptors,inhibits KATP channels and stimulate insulin secretion. It is rapidly absorbed and the bioavailability is 72%. The absorption is more rapid when the drug is orally administered before the meal. Peak plasma concentrations is within 1 h and the half-life is 1.8 h. It is metabolized mainly by CYP2C9 and CYP3A4 cytochrome P450 enzymes and eliminated primarily by the kidney. It is rapidly bind to plasma proteins and has small volume of distribution. (Guardado-Mendoza et al., 2013).

Herbs

In India, due to poverty and malnutrition, there is increased usage of herbal products as it reduces the healthcare cost of the Indian people. Ayurveda is the oldest traditional system of medicine in India. It prefers worldwide consumption of different herbal medicines containing phytochemicals and therapeutic properties to cure various chronic diseases (Ali et al., 2008). As herbal medicines are continuously influencing human life, researchers are interested in evaluating health-related issues by using medicinal plants with prescribed drugs. Amongst different commonly used medicinal plants in Rajasthan, India, the plants of our interest in this study belong to *Prosopis* species containing anti-diabetic properties.

Prosopis juliflora

Prosopis juliflora, commonly referred as Mesquite, belongs to the family Leguminosae (*Fabaceae*) (Dave & Bhandari, 2013) & (Patnaik et al., 2017). It is grown in arid and semi arid regions of America, Africa, and Asia. It is a traditional medicinal plant in India, popularly named as angaraji babul, Kabuli kikar, vilayati babul, vilayati khejra, and vilayati kikar with versatile therapeutic properties (Dave & Bhandari, 2013). It is virtually used as antibacterial, antifungal, antagonistic, anti-tumor, antioxidant, antidiabetic, antihelminthic, antipyretic, antiulcer, antigiardial & amoebicidial, and antipustule properties used to cure different chronic diseases (Ukande et al., 2019). *P. juliflora* exists as a tree with a maximum height of 12 m (20 m in favorable conditions) and also exists as a shrub of 3 m, respectively (Dave & Bhandari, 2013). It is a xerophytic plant that grows in arid and semi-arid regions of the world where other species cannot (Peter Odero, 2017). It can extremely survives in a harsh environment and thrive in different soil conditions (sandy, stony, heavy clay, and alkaline soil) (Patnaik et al., 2017). An

early report by (Henciya et al., 2017) states that almost every part of *P. juliflora* contains phytochemicals of various pharmacological properties that are beneficial for treating different human health hazards. The plant is used in treating pain disorders, eye problems, wound healing ,and dermatological or digestive ailments (Lakshmibai, 2015). Pods part of *P. juliflora* produce lepidopteran larval motility that increases the antioxidant and immune system and beneficial in managing diabetes (Berwal et al., 2019). Leaves of this plant contain antibacterial and antifungal properties that are effective in curing headache, painful gums, and bladder infection (Lakshmibai, 2015). The trunk part of *P. juliflora* is short and twisted with a diameter of ~65 cm and used to make timber, building poles, furniture, charcoal, and firewood (Dave & Bhandari, 2013) & (Patnaik et al., 2017). The wood of the plant contains cellulose, hemicellulose, and lignans and bark is grey or brown and rough or fibrous containing antioxidant and anti-inflammatory properties (Patnaik et al., 2017) & (Berwal et al., 2019). *P. juliflora* is beneficial in treating different environmental hazards, used as a source for fuel, food, medicine, biopesticides, bio sorbent, and carbon activation (Patnaik et al., 2017).

Figure 1 : Prosopis juliflora (Basu et al., 2017)

Phytochemicals present in *P. juliflora*

P. juliflora contains various chemical constituents such as terpenes, flavonoids, alkaloids, and phenolic compounds that show therapeutic properties and can alter the physiological actions of the body (Ukande et al., 2019). Terpenes and terpenoids are known as isoprenoids (Cox-Georgian et al., 2019). They are natural products found mainly in plants and animals (Gershenzon & Dudareva, 2007) and are involved in the fragrance, pigmentation, and taste of the

plant (Cox-Georgian et al., 2019). They contain various medicinal properties such as anti-insect, antimicrobial, antiplasmodial, antiviral, anticancer, antidiabetic, and antidepressant (Cox-Georgian et al., 2019). The phytochemical analysis of different parts of *P. juliflora* studied by (S. Singh, 2012) showed the presence of a high concentration of terpenes in leaves and pods followed by flowers and roots. (Berwal et al., 2019) showed the presence of terpenoids in the pods of the plant. Then further this compound, showed hypoglycemic effects on the body used for the treatment and management of diabetes mellitus. Tannins are group of phenolic compounds widely distributed in plants (Hassanpour, S., Maheri-Sis, N., Eshratkhah, B., & Mehmandar, 2011). They are used as antiseptic, antimicrobial, and antioxidants agents (S. Singh, 2012). The phytochemical analysis of (Khandelwal et al., 2016) & (S. Singh, 2012) showed the presence of tannins in the leaf and pod part of *P. juliflora.* Alkaloids are important secondary metabolites derived naturally from plants (Debnath et al., 2018). They have various medicinal properties that include drugs such as nicotine, morphine, quinine, atropine, cocaine, and caffeine (Keiser, 2016). Alkaloids isolated from the plant *Prosopis juliflora* are juliflorine, seco-juliprosopinal, juliprosine, and isojuliprosine with antioxidant, antifungal, and anti-bacterial properties (Ukande et al., 2019). Flavonoids are natural products, widely exist in plants (fruits and vegetables) (Panche et al., 2016). They occur in large amount in the leaves lesser amount in the flowers of the *Prosopis juliflora* (Khandelwal et al., 2016). A number of flavonoids have been isolated from the *P. juliflora* plant and they include catechin, mesquitols, epi-catechin, 6 flavones-apigenin, luteolin, quercetin 3-O-diglycoside etc from different parts of the plant (Dave & Bhandari, 2013). Mesquitol is also an antioxidant and belongs to the group flavan-3-ol of flavonoids. It has free radical scavenging and α-glucosidase inhibitory properties capable of treating cancer and diabetes (Peter Odero, 2017). (Azam et al., 2011) compared the antioxidant potential of mesquitol with two commonly used drugs probucol and α-tocopherol and found mesquitol is better than both the drugs. (Sirmah et al., 2011) found mesquitol to be abundant in the heartwood of the *P. juliflora*. Catechin or epigallocatechin-3-gallate is a major tea flavonoid. It is naturally present in wine, fruits, and cocoa showing that they have anti oxidative and anticancer physiological properties (Moridani et al., 2001). Small amounts of catechin and epichatechin have been found in the heartwood of *P. juliflora* (Azam et al., 2011).

Prosopis cineraria

Prosopis cineraria is commonly known as Khejri, belongs to the family Fabaceae (Soni et al., 2018). It is mostly cultivated in Western and Southern Asia including Afganistan, Iran, India, Oman, Saudi Arabia, and Pakistan. It is a state tree of Rajasthan, popularly named as Sangri, sami, mesquite, shami, jhand, khijado, shemi, jambi, candy, khejari, ghaf. It has antibacterial, antihyperglycemic, antihyperlipidemic, antidepressant, bronchodilator, vasodilatory, detoxifying, anticancer, analgesic, antidiarrhoeal, anticonvulsant, antioxidant, and antimicrobial therapeutic properties. It is a medium size tree (5 to 10 m height) grows in dry and arid regions of Arabia and also in some regions of India such as Rajasthan, Haryana, Punjab, Gujarat, and Uttar Pradesh. The crude extract of this plant is used in preventing protein and mineral deficiency. All parts of the parts are considered beneficial with different nutritional values used in the prevention and treatment of various diseases. The bark of the tree is used for the preparation of medicines mostly for stomach, skin, and eye problems. Leaves of the plant have antibacterial, antihyperlipidemic, antioxidant fungicidal and insecticidal activities. Pods of P. cineraria are brown on ripening, locally called as Sangri, and are used to prevent protein and mineral deficiency (Pareek et al., 2015). The gum part of the tree is nutritive and good in taste used by a pregnant woman at the time of delivery and paste of flowers acts as anti-diabetic agents (L. Kumar et al., 2018).

Figure 2: Prosopis cineraria

Phytochemicals present in *P. cineraria*

P. cineraria contain various chemical constituents such as tannins, flavonoids, steroids, and alkaloids etc. Flowers contain patuletin glycoside patulitrin, sitosterol, spicigerine, Flavone derivatives Prosogerin A and Prosogerin B (Girase et al., 2016) & (Vaza & Sciences, 2018). Leaves contain steroids like campesterol, cholestrol, sitosterol and stigmasterol, actacosanol, hentriacontane, methyl docosanoate, Diisopropyl-10, 11-dihydroxyicosane- 1, 20-dioate, Tricosan-1-ol, and 7, 24-Tirucalladien-3-one along with a piperidine alkaloid spicigerine. Seeds contain Prosogerin C, Prosogerin D, Prosogerin E, Gallic acid, patuletin, patulitrin, luteolin, and rutin (Pareek et al., 2015). Dried pods contain 3-benzyl-2-hydroxy-urs-12-en-28-oic acid, maslinic acid 3-glucoside, linoleic acid, prosphylline, 5, 50-oxybis- 1,3-benzendiol, 3,4,5, trihydroxycinnamic acid 2- hydroxy ethyl ester and 5,30,40-trihydroxyflavanone 7- glycoside (Liu et al., 2012). Bark contain Hexacosan-25-on-l –ol, a new keto alcohol alongwith ombuin and a triterpenoid glycoside.vitamin K1, n-octacosyl acetate, the long chain aliphatic acid. Presence of glucose, rhamnose, sucrose and starch (Pareek et al., 2015).

Table 1: - Phytochemicals present in *Prosopis* species -

S.No.	Compound Name	Source
	Flavonoids	
1	Patulitrin	*P. cineraria*
2	Prosogerin A	*P. cineraria*
3	Prosogerin B	*P. cineraria*
4	Prosogerin C	*P. cineraria*
5	Prosogerin D	*P. cineraria*
6	Prosogerin E	*P. cineraria*
7	Patuletin	*P. cineraria*
8	Luteolin	*P. cineraria*
9	Apigenin	*P. juliflora*
10	Apigenin 6,8-di-C-glycoside	*P. juliflora*
11	Chrysoeriol 7-O-β-D-glucoside	*P. juliflora*

12	Luteolin 7-O- glucoside	*P. juliflora*
13	Kaempferol 3-O-methyl ether	*P. juliflora*
14	Isorhamnetin 3-O-glucoside	*P. juliflora*
15	Isorhamnetin 3-O-rutinoside	*P. juliflora*
16	Quercetin 3-O-rutinoside	*P. juliflora*
17	(-)-Mesquitol	*P. juliflora*
18	Ellagic acid	*P. juliflora*
Alkaloids		
1	Spicigerine	*P. cineraria*
2	Dasycarpidan-1-methanol,acetate (ester)	*P. cineraria*
3	3-Butylindolizidine	*P. cineraria*
4	Prosophylline	*P. cineraria*
5	N- Methyljulifloridine	*P. juliflora*
6	Julifloridine	*P. juliflora*
7	Prosoflorine	*P. juliflora*
8	Juliprosinene	*P. juliflora*
9	Juliprosine	*P. juliflora*
10	Secojuliprosopinal	*P. juliflora*
11	2,4-Diphenyl-6,7,8,9 – tetrahydro-5H-cyclohepta (D) pyrimidine	*P. juliflora*
12	Cassine	*P. juliflora*
Steroids		
1	Cholesterol	*P. cineraria*
2	7,24-Tirucalladien-3-one	*P. cineraria*
3	Campsterol	*P. cineraria*
4	Stigmasterol	*P. cineraria*
5	β-Sitosterol	*P. cineraria*
6	Stigmasta-4,6-dien-3-one	*P. cineraria*
Fatty acids and derivatives		
1	(Z)-13-Docosenamide	*P. cineraria*

2	9-Hexadecenoic acid	*P. cineraria*
3	Palmitic acid	*P. cineraria*
4	Stearic acid	*P. cineraria*
5	Oleic acid	*P. cineraria*
6	Linoleic acid	*P. cineraria*
7	Heneicosanoic acid	*P. cineraria*
8	Methyl heptacosanoate	*P. cineraria*
Phenolic compounds		
1	4,4'-(1-Methylethylidene) bis – phenol	*P. cineraria*
2	Gallic acid	*P. cineraria*
3	Rutin	*P. cineraria*
4	Paeonol	*P. cineraria*
5	4- Hydroxy benzoic acid	*P. cineraria*
6	2,4-Bis (1-phenylethyl) phenol	*P. juliflora*
7	2,4,6-Tris-(1-phenylethyl) phenol	*P. juliflora*
Terpenoids		
1	Phytol	*P. cineraria*
2	Squalene	*P. cineraria*
3	3 -Benzyl-2-hydroxy-urs-12-en-28-oic acid	*P. cineraria*
4	Rhodopin	*P. cineraria*
5	Rhodoxanthin	*P. cineraria*
6	β – Carotene	*P. juliflora*
Phenyl propanoids		
1	(–)-Lariciresinol	*P. juliflora*
2	Syringin	*P. juliflora*
3	Ferulic acid	*P. cineraria*
4	Methyl 4-hydroxycinnamate	*P. cineraria*
5	Methyl 2-methoxy-5-hydroxycinnamate	*P. cineraria*
6	O-Coumaroylglycerol	*P. cineraria*

Tetra pyrroles		
1	Pheophytin A	*P. juliflora*
2	Pheophytin B	*P. juliflora*
They also contain other compounds such as alcohol, esters, diketones, alkanes, heterocyclic compounds, etc.		

Research works on *Prosopis* species. –

S.No.	Study	Name of the Research group
1	the ethanolic extract of *Prosopis cineraria* pod contains potent bioactive phytocompounds might be inhibit HMG – CoA reductase .	(Ram et al., 2020) a
2	*P. juliflora* fruit extract contain terpenoids and fatty acids phytochemicals that are utilized in diabetes, cancer, wound healing, inflammation, and microbial infection management.	(Berwal et al., 2019)
3	Pods Ethyl acetate fraction of *Prosopis cineraria* displayed excellent anti-hyperglycaemic activity in-vitro and in-vivo and should be evaluated further to develop as a promising drug for management of diabetes mellitus	(M. Kumar et al., 2019)
4	Phytoconstituents of pod extract of *P. cineraria* resolve insulin induced neurological complications as it inhibit DPP-4 and other target enzymes.	(Ram et al., 2019) b
5	The use of *P. juliflora* bark for synthesis of AgNPs proved the anticancer activity of AgNPs .	(Arya et al., 2018)

6	*P. juliflora* pods contain Terpenoids a valuable source of anticancer, antitumor, chemopreventive compounds.	(Malik et al., 2018)
7	Stem bark of chloroform fraction *P. cineraria (Cfpc)* possesses various phytocompounds that may be responsible for its antidiabetic property therefore it could be used as a safer complementary drug in the management of diabetes	(Soni et al., 2018)
8	The leaf extracts of *P. juliflora* showed inhibitory activity against different species of bacteria result obtain states the use of leaf extract of the plant as antibacterial agents.	(Badri et al., 2017)
9	*Datura metel* and Seeds and leaves extract of *Prosopis juliflora* contain antibacterial, antifungal, anti-inflammatory properties that will be useful in treating people affected with excess dandruff and used to form antidandruff shampoo.	(R. S. A. S. Kumar et al., 2017)
10	*Prosopis cineraria* produce several compounds including alkaloids, tannins, saponins, flavonoids, proteins, coumarins and resins. The constituents of leaves and stem bark of *Prosopis* have several medicinal properties and can be utilized for the treatment of various diseases. So, it can be concluded that this plant can be used for treating various ailments without any side effects.	(Pathak & Kumar, 2017)
11	Aqueous and ethanolic extract of *Prosopis cineraria* contain bioactive compounds susch as flavonoids, glycosides, phenolic compounds that may cause depletion of lipid content from peripheral tissues.	(Jain & Surana, 2016)

12	Qualitative analysis of the total metabolite present in different parts of the plant showed leaf and pod to be the richest source of plant metabolite. Phytochemical analysis of the extracts revealed presence of carbohydrates, proteins, tannins, flavonoids, alkaloids, terpenes and steroids in most of the parts of *P. cineraria.*	(Khandelwal et al., 2016)
13	Phytochemical constituents like flavonoids, phenolic compounds, alkaloids and other secondary metabolites are present in leaf extract of *P. juliflora.* Leaf extract of the plant contain antioxidant property.	(Lakshmibai, 2015)
14	The antioxidant compound mesquitol is present in the wood part of *P. juliflora.*	(Azam et al., 2011)

Herb drug Interaction (HDI)

Herbal medicines are primary health care supplements for self – medication (Fasinu et al., 2012) & (Vaidya & Devasagayam, 2007). Patients with chronic diseases prefer concomitant administration of herbal medicine with prescribed allopathic drugs without consulting with their healthcare providers. This combinational therapy can change the drug concentration level and causes adverse effects in the human body (Shaikh et al., 2020). HDI is considered as an important clinical therapy to create awareness among people about the risk factors of this combinational therapy (Fasinu et al., 2012). The ability of intestinal and hepatic CYP enzymes metabolize various xenobiotic compounds that are responsible for further HDI studies (Quintieri et al., 2008).

Mechanism of HDI

Mechanism of HDI involves the pharmacodynamic and pharmacokinetic properties of the drug (Nanjappan et al., 2018). Pharmacodynamic properties alter the pharmacological reactions through additive, synergistic, and antagonistic actions (Borse et al., 2019). While pharmacokinetic interactions alters the absorption, distribution, metabolism, and excretion (ADME) of the drug that results in changing the drug metabolite levels (Nanjappan et al., 2018). Figure 2 describes Pharmacokinetic interaction (ADME). It involve inhibition or induction of drug-metabolizing enzymes (DMEs) mainly Cytochrome P450 (CYP) and drug transporters such as P-gp which results in increasing or decreasing plasma levels of the drug (K. Kapoor & Singla, 2015). Therefore, pharmacokinetic interactions are more complicated as compared to pharmacodynamics. However, also there is a complex HDI which involves both pharmacodynamic along with pharmacokinetic properties (Borse et al., 2019).

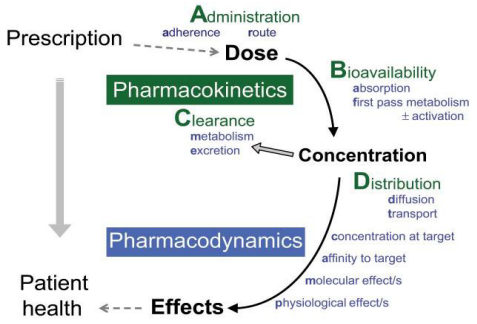


Figure 3: Pharmacokinetic interaction (ADME)

Drug Metabolizing Enzymes (DMEs)

DMEs are known as monooxygenase and mixed-function oxidase. They contain enzymes such as cytochrome P450, UDP –glucuronosyl transferases, Sulfotransferases, and N-acetyltransferases, etc. (Sheweita et al., 2016).

Cytochrome P450 (CYP) enzymes are a pervasive superfamily of hemoprotein monooxygenases that metabolize vital chemical compounds and detoxify xenobiotic drugs (Munro et al., 2018).

They are called cytochromes P450 because they are coloured proteins, and absorb light at wavelengths near 450 nm when the haem iron is reduced and complexed with carbon monoxide (Timbrell & Marrs, 2009). The CYP enzymes classified into 18 families and 43 sub-families (Wang & Chou, 2010). CYP 1, 2, and 3 families that include sub-families (1A2, 2A6, 3A4, 3A5, 2C9, 2C19, 2D6, and 2E1) are the most used enzymes for metabolizing xenobiotic drugs (Shaikh et al., 2020). CYP1A1 and CYP1A2 are members of the CYP1A subfamily that constituent 50% of hepatic CYP content. CYP1A1 is present in the extra-hepatic tissues of the kidney, intestine, and lungs (Martignoni et al., 2006). CYP2B6 enzymes are members of the CYP2B subfamily involves in drug metabolism (Pavek & Dvorak, 2008). CYP2C are the most abundant CYP enzymes involving CYP2C8, 2C9, and 2C19 for metabolizing xenobiotic compounds. About 20% of the total CYP2C enzyme subfamily is present in the human liver (Lewis, 2004). In the CYP2E subfamily, CYP2E1 is the most active enzyme for metabolizing drugs such as paracetamol, chlorzoxazone, and enflurane (Leclercq et al., 2000). CYP3A enzyme subfamily constitutes 40% of total CYP content in the human liver. CYP3A4 are members of the CYP3A subfamily that metabolize modern drugs (Ferguson & Tyndale, 2012) & (D. Singh et al., 2011).

Phase I is the alteration of biologically active compounds of xenobiotic drugs (Timbrell & Marrs, 2009). This phase involves oxidation, reduction, hydrolysis, and hydration reactions that are mediated by CYP enzymes (Fasinu et al., 2012).

Oxidation - The oxidation reaction is mediated by the CYP enzyme system. This reaction subdivides into aromatic hydroxylation of carbon, aliphatic hydroxylation of carbon, alicyclic hydroxylation of carbon, heterocyclic hydroxylation, epoxidation, N-,S- and O-dealkylation, N-oxidation, N-hydroxylation, S-oxidation, desulfuration, dehydrogenation, cleavage of esters and deamination reactions (Timbrell & Marrs, 2009).

Reduction - The reduction reaction catalyzed by mammalian microsome, cytosolic reductase, and gut bacteria. It also involves CYP450 and NADPH quinone oxidoreductase enzymes for the reduction of xenobiotics. This reaction mainly catalyzes nitro and azo groups and also reduces aldehydes, ketones, disulfides, sulfoxides, quinones, N-oxides, alkenes, halogenated hydrocarbons and certain metals (Timbrell & Marrs, 2009).

Hydrolysis - This reactions include esterases such as - hydrolyse carboxylic acid esters, thioesters, cholinesterases, neuropathy target esterase, and carboxylesterases. An ester with amidase activity also mediates hydrolysis reactions (Timbrell & Marrs, 2009).

Hydration - This reaction includes enzyme epoxide hydrolase located in several forms in Smooth Endoplasmic Reticulum near the CYP450 enzyme system (Timbrell & Marrs, 2009).

Phase II metabolic process includes uridine diphosphoglucuronosyl transferase (UGT), *N*-acetyl transferase (NAT), glutathione *S*-transferase (GST), and sulfotransferase (ST) mediate the attachment of polar and ionizable groups to phase I metabolites to support their elimination (Fasinu et al., 2012).

Drug Transporters (DTs)

DTs are large membrane-bound proteins widely expressed in body tissues. They are beneficial in reducing drug toxicity by allowing the drug to reach its target site at adequate concentration without accumulating in other body tissues (Degorter et al., 2012). They also play a role in the ADME of xenobiotics (Nanjappan et al., 2018). DTs are of two types such as – ATP binding cassette transporters (ABC) and Solute Carrier (SCL) transporters.

ATP binding cassette transporters (ABC) are present on the luminal membrane of enterocytes. They limits the intestinal absorption of most prescribed drugs (antibiotics, immunosuppressants, anticancer, and cardiovascular drugs, etc.) and also focuses on the drug bioavailability (Estudante et al., 2013). P-glycoprotein (P-gp), Breast cancer resistance protein (BCRP), and multidrug resistance-associated protein (MRP) are the members of this drug transporters family (Degorter et al., 2012).

P-glycoprotein (P-gp) - MDR1 drug - transporting P-glycoprotein is an efflux transporter localized in the gut (Estudante et al., 2013). It is expressed in the apical membrane of enterocytes, hepatocytes, kidney proximal tubules, and in endothelial cells. It protects body tissues from xenobiotic drugs. Substrates of P-gp are hydrophobic and cationic includes HIV protease inhibitors, calcium channel blockers, and anticancer drugs of the vinca alkaloid,

anthracycline, and taxane classes (Cascorbi, 2011). It inhibits by verapamil, ritonavir, and cyclosporine and reduces the absorption of xenobiotics (Chen et al., 2005).

Solute Carrier (SLC) transporters – They are the group of drug transporters that mediate solute influx and efflux of substances such as membranes ions, nucleotides, and sugars across plasma and intracellular membranes (Hediger et al., 2004). Different types of SLC are Organic anion transporting polypeptides (OATPs), Nucleotide transporters (NT), Monocarboxylate transferases (MCT), Organic ion transporters, and Proton coupled oligopeptide transporter (POT) (Nanjappan et al., 2018).

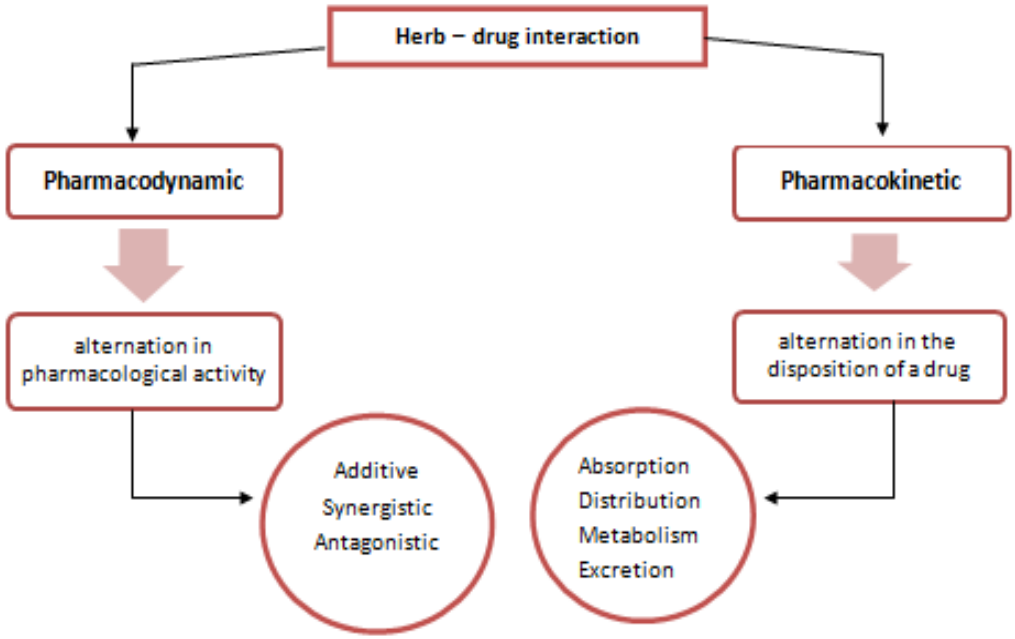


Figure 4: Mechanism of HDI

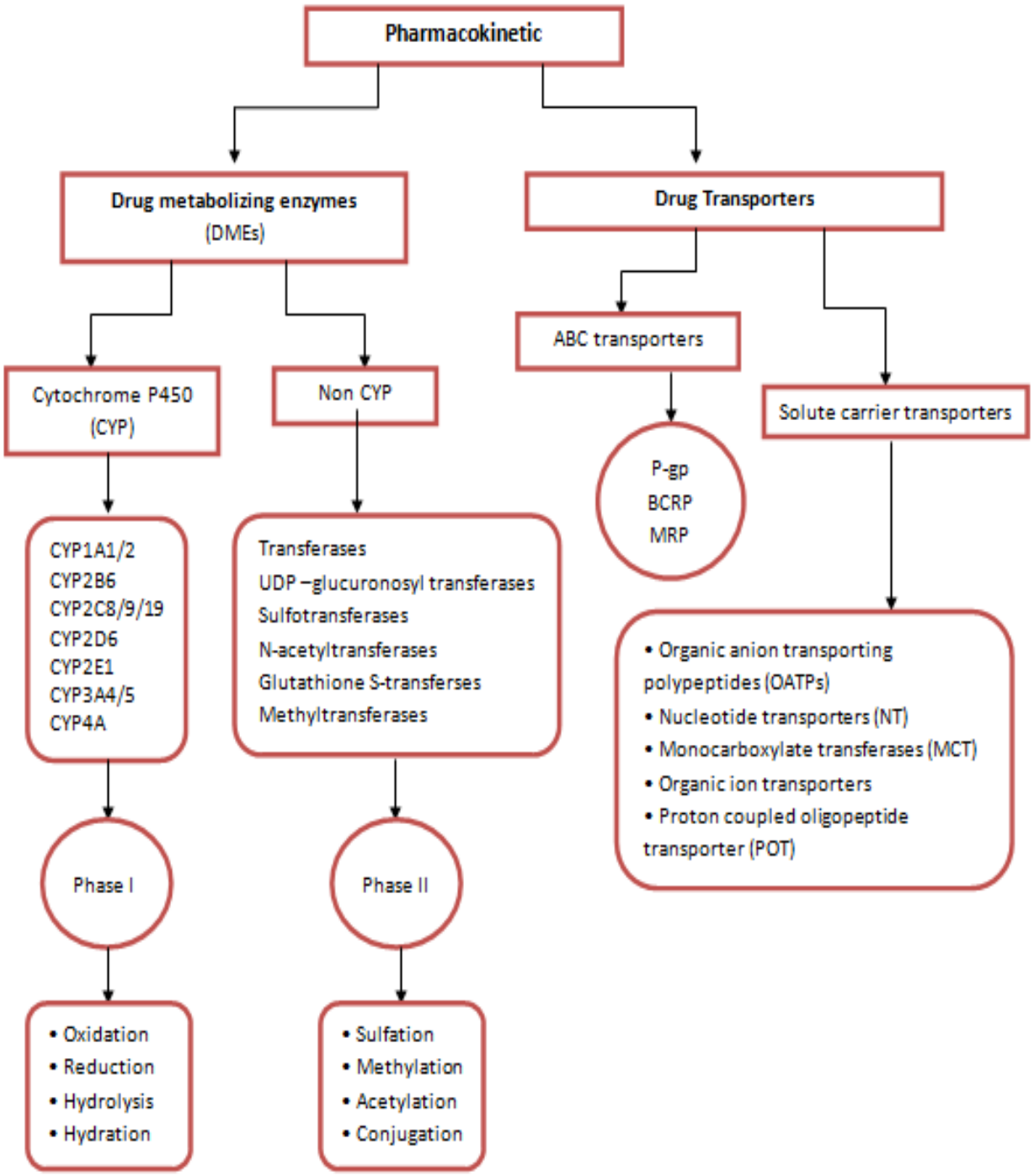


Figure 5 : Classification of pharmacokinetic properties

Research work on HDI with Oral Antidiabetic drugs -

S.No.	Study	Name of the Research group
1	Nateglinide and pomegranate if given together could synergize in their anti-diabetic potential and significantly reduce diabetes associated complications.	(Chakraborty et al., 2017)
2	Consumption of St John's wort had no significant effect on pharmacokinetics and pharmacodynamics of repaglinide.	(Fan et al., 2011)

Research gap –

From review of literature or above properties, now it is clear that HDI is an important parameter to be study for any concomitant administration of plant with drugs. In this present study we plant to study the herb drug interaction of common Indian herbal species *Prosopis. (Prosopis juliflora & Prosopis cineraria)* with commonly prescribed Antidiabetic drug class Meglitinides as it is suggested that there is no research work done on it.

Objective

- To study pharmacodynamics parameters of additive, synergistic, and antagonistic of DMEs and DTs.
- To study pharmacokinetics parameters of DMEs and DTs.

Methodology

Collection of plant species

Fresh fruits and pods of *P. juliflora* and Stems and pods of *P.cineraria* will be collected.

Preparation of plant extract

Ethanol extract of fruits of *P. juliflora* will be prepared by using soxhlet apparatus and the chemical analysis of the fruit extract of the plant will be carried out by GC-MS technique. Oil from dried pods of *P. juliflora* will be extracted by using soxhlet apparatus. Chloroform fraction of Stem bark of *P. cineraria* will be extract by using soxhlet apparatus and then it will be suspended in 0.5% DMSO (dimethyl sulfoxide) in distilled water for the assessment of Antidiabetic activity. Dried pods of *P. cineraria* will be extract with ethanol soxhlet extractor and the chemical analysis of the pod extract will be carried out by LC-MS technique.

Experimental animals

The animal experimentation protocol will be approved by the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). Swiss Albino mice of either sex, roughly of same age and weight of between (25- 30 g) will be used to study Antidiabetic activity. They will be maintained under standard conditions of humidity (55 ± 5%), temperature (25 ± 3 °C), and light (12-h light: 12-h dark cycle). The animals will be fed with conventional diets and water ad libitum.

Cytotoxicity assay

To determine the toxicity and the optimum dose of the *P. juliflora* and *P. cinneraia* herb extracts, cytotoxicity will be measured by MTT assay/Trypan blue dye exclusion assay/Colony formation assay.

Antidiabetic study of the plant (using Biochemical Parameters)

Diabetes will be induced by a single intraperitoneal injection of Streptozotocin (STZ) (55 mg/kg b.wt), freshly prepared in 0.1M sodium citrate buffer (pH 4.5) after overnight fasting. Animals will be fed with 5% glucose solution for 12 h to avoid hypoglycaemia.

Group I: No treatment will be given

Group II: STZ only

Group III: STZ + Plant extract of P. juliflora

Group IV: STZ + Plant extract of P.cineraria

Group V: STZ + Oral Antidiabetic Drug

Group VI: STZ + Plant Extracts + Drug

The fasting blood glucose level will be measured using the diabetes test-strips (Glucometer) and the mice showing moderate diabetes, having hyperglycemia will only be selected for further study. Estimation of other biochemical parameters such as glycosylated hemoglobin (HbA1c), serum lipid profile tests such as total cholesterol, triglycerides, LDL-Cholesterol, HDL-Cholesterol will be determined by using commercially available kits. Glycogen content in liver will also be estimated by using anthrone reagent method.

Determination of metabolites' level of the drug and the plant extract (in blood plasma)

In-vitro: Assessment of DMEs activity on Liver Microsomes by Erythromycin-N-demethylation Assay

In-vivo: Drug Metabolite Study in mice (blood plasma) by using HPLC and LC-MS.

Intestinal and hepatic level -

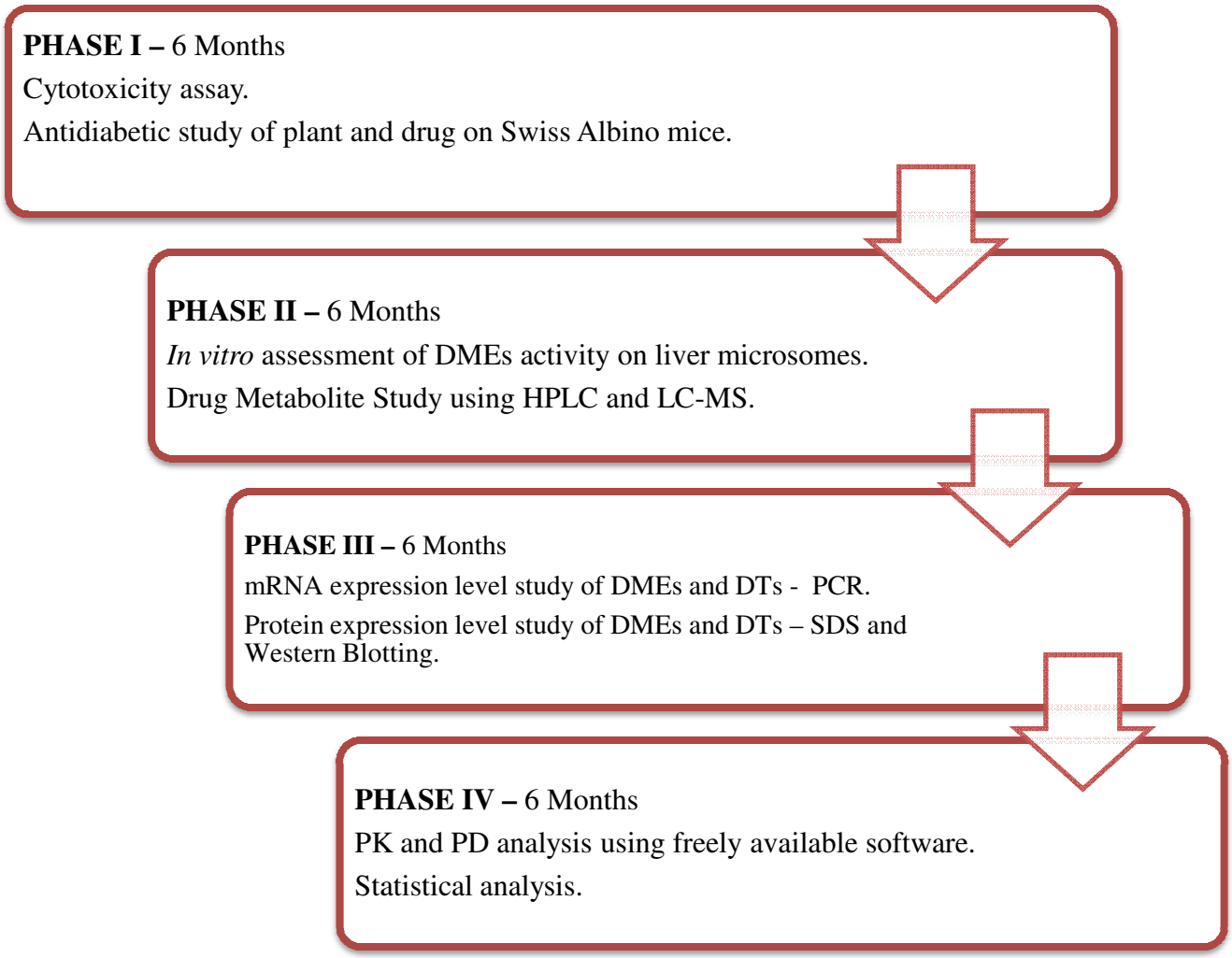
The mRNA expression level study of DMEs and DTs by using PCR technique.

Protein expression level study of DMEs and DTs by using SDS-PAGE and Western Blotting technique.

Pharmakokinetic and statistical analysis

The pharmacokinetic and statistical analysis will be done using any open source software.

Plan of work


PHASE I – 6 Months
Cytotoxicity assay.
Antidiabetic study of plant and drug on Swiss Albino mice.
PHASE II – 6 Months
In vitro assessment of DMEs activity on liver microsomes.
Drug Metabolite Study using HPLC and LC-MS.
PHASE III – 6 Months
mRNA expression level study of DMEs and DTs - PCR.
Protein expression level study of DMEs and DTs – SDS and Western Blotting.
PHASE IV – 6 Months
PK and PD analysis using freely available software.
Statistical analysis.

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